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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,836	06/12/2001	Laurent F A Hennequin	P.278065	6411

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,836	HENNEQUIN ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-14 and 16-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-10,13,14 and 16-19* is/are rejected.

7)☒ Claim(s) *11 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of 5-3-06 has been fully considered. While applicant's argument on the term "thiophenoxy" is persuasive, the equivalent teaching in Myers et. al. (US'969) is still pertinent, and so the 103 rejection based on Myers et. al. is maintained without relying on ***Hawley's* Condensed Chemical Dictionary**.

Applicant's argument on the 103 rejection based on Manning et. al. (WO'321) is also persuasive. Thus, said rejection is withdrawn herein.

New issues of 112/1st and 2nd paragraphs are noted and presented below.

Claims 1-4 and 15 are cancelled.

Claims 5-14 and 16-19 are pending.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 13 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The above claims recite: "A method for producing an antiangiogenic and/or vascular permeability reducing effect..." which has indefinite metes and bounds. Defining a disease(s) by its (their) underlying cause renders the scope of intended uses indeterminate since the claim language may read on diseases not yet known to be caused by or

affected by such action or in ways not yet understood. The test for determining compliance with 35 USC 112/2nd paragraph is whether applicants have clearly defined "their" invention, not what may be discovered by future research as this type of claim language clearly requires.

Claim Rejections - 35 USC § 112, First Paragaph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Scope of Enablement:** Claims 5-10, 13, 14 and 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the making and using of compounds of formula II wherein:

a. ring C is ***pyrazolyl***, and

b. R^2 (at the 7-position) represents *methoxyethoxy-, 3-morpholinopropoxy-, 3-(4-methylpiperazin-1-yl)propoxy, 1-methylpiperidin-4-ylmethoxy,(2- methoxyethoxy)ethoxy, 2-(imidazol-1-yl)ethoxy, 2-(1,2,3-triazol-1-yl)ethoxy,*

does not reasonably provide enablement for the making and using of compounds of formula II wherein ring C is another 5- or 6-membered heterocyclic moiety, and R^2 represents other groups selected from the list of R^5X^1-. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 18 recites: "A compound of the formula II wherein ring C is a 5-6-membered heterocyclic moiety which may be saturated or unsaturated, which may be aromatic or non-aromatic, and which contains 1-3 heteroatoms selected independently from O, N and S;...." Clearly the scope of ring C covers a large number of heterocyclic moieties. The definition of R^2 as R^5X^1 including an extensive list of substituents. Thus, the definitions of ring C and R^2 render the scope of claim 18 unduly broad.

Claims 5-10, 14, 16, 17 and 19 depend on claim 18, and carry over the broad scope of C, R^2 or both.

Claims 13 and 17 recite: "A method for producing an antiangiogenic and/or vascular permeability reducing effect..." which covers the treatment of various diseases having different etiologies and manifestations such as: cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's

sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation (see specification page 2, lines 15-31). Thus, the scope of the claimed method is also unduly broad.

The amount of direction or guidance presented: Regarding the preparation of compounds of formula II, the specification only provides the starting material for ring C as *pyrazole* (see page 40, first paragraph, the details of how to make formula IV – an intermediate carrying ring C as *pyrazole*). As for the substituents of R^2, a limited number (as listed above) is found in the working examples. The specification is silent as to the availability of necessary reactants needed to prepare a compound of formula II with ring C as other heterocyclic moieties and/or R^2 as a substituents outside of working examples. Note, **In re Howarth** 210 USPQ 689; **Ex parte Moersch** 104 USPQ 122, for the need to show starting material sources commensurate with the claims' scope.

Regarding the biological activity, the specification only details various bioassay methods without indicating which compounds have been tested. Assuming all compounds in the working examples have been tested, their activity cannot be extrapolated to other compounds of formula II wherein ring C is other than *pyrazole*, and R^2 is other than substituents listed above as there is no evidence of recognized biological equivalency for such diverse groups.

Thus, the specification does not provide sufficient enablement commensurate with the broad Markush group of formula II, and the broad method of antiangiogenic, and vascular permeability reducing effect.

The state of the prior art: Typically, quinazoline compounds are known to treat solid tumor, rheumatoid arthritis or preventing transplant rejection as evident by **Myers et. al.** (US'969 B1). Myers' quinazoline compounds; however, have simple substituents at the 6- and 7-positions, and not as complicated as those represented by the instant R^2. Thus, the state of the prior art does not provide adequate enablement for making compounds in commensurate with the scope of formula II and use them in a method of antiangiogenic, and vascular permeability reducing effect.

The relative skill of those in the art: Even with the advanced training, the skilled medicinal chemist and/or clinician would have to carry out extensive research to make an array of compounds of formula II, and select an effective compound from such a large Markush group for antiangiogenic, and vascular permeability reducing effect. Not only one has to determine the inhibitory activity on tyrosine kinase, VEGF, FGF or EGF receptor, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Given a large Markush group of the claimed formula II, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals.

In the instant case, the specification does not provide starting materials for making compounds of formula II with various heterocyclic ring and complicated substituents. It also fails to provide biological data for using the claimed compounds in a method of antiangiogenic, and vascular permeability reducing effect. Thus, with the large Markush group of formula II, without the guidance for starting material sources of ring C and many groups in R^2, undue experimentation is necessary for making such an array of compounds as well as establishing biological activity for those compounds as inhibitors of VEGF or receptor tyrosine kinase.

Regarding method claims 13 and 17, *in-vitro* activity of the tested compounds does not warrant the *in-vivo* activity for antiangiogenesis and vascular permeability reducing effect which covers the treatment of a myriad of diseases. The unpredictability in the treatment of angiogenesis is noted by **Brower** in the following excerpt:

> "Many approaches for inhibiting angiogenesis are still very early in development..., and it is difficult to predict which target and which treatment type will prove the most effective...
>
> As such, drugs that target growth factors, growth factor receptors, and proteases (e.g., MMPs) present on both ECs and tumor cells may not represent optimal targets...The lack of specificity of these treatments not only increases the likelihood of resistance, but also can result in potential toxicities and side effects,...
>
> Furthermore, the redundancy and crosswalk between proteins that signal the angiogenic cascade present other problems for treatments directed at single growth factors. For example, in some tumors, when VEGF is downregulated, bFGF is upregulated, possibly neutralizing the effect of the former..." (page 968, the section of "Weighing the options").

Given a broad scope of method claims, applicants' sole reliance on *in-vitro* or screening tests does not sufficiently guide the skilled clinician to treat diseases related to angiogenesis and vascular permeability without undue experimentation. Also, see ***Hoffman v. Klaus*** 9 USPQ 2d

1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 5-9, 14, 16-19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Myers et. al.** (US 6,645,969 B1).

While applicant is correct on the meaning of the term "thiophenoxy", the equivalent teaching in US'969 cannot be ignored. Besides the two quinazoline compounds having "thiophenoxy" mentioned in the previous action, Myers et. al. also list other quinazoline compounds with a heterocyclic ring corresponding to the instant ring C, namely:

4-(thien-3-yl)-6,7-dimethoxyquinazoline;

4-(pyrazol-3-ylamino)-6,7-dimethoxyquinazoline hydrochloride.

While the above species do not anticipate the instant scope in view of the proviso for R^2 in claim 18, they are obvious variants since Myers et. al. teach other substituents at the 7-position on the quinazoline ring as well – see definition of R_7 which includes alkylthio, hydroxyl, cycloalkyl, etc.

Myers et. al. also teach different linking groups represented by X which includes a bond, –O-, -S-, -NH, etc., and various aryl as well as heteroaryl ring represented by Ar. Also, see species in columns 14-16, which collectively teach various aspects of applicant's invention.

With the equivalency teaching provided in the definition of variables X, Ar of the disclosed formula I on column 3 of US'969, it is clear that –O-, or –S- can replace the amino group at the 4-position (see the definition of X on line 21). Also, heterocyclic moieties such as: *thienyl,* or *pyrazolyl* can replace the phenyl group in "thiophenoxy" (phenyl-S-). Likewise, there is also equivalency teaching for substituents at the 6- and 7-position (corresponding to the instant variable R^2 or R^{2a}), in which *allkylthio, hydroxyl, carboxy, carbalkoxy* can replace the alkoxy group (see definitions of R_7 on column 3, line 36).

Thus, it would have been obvious to make compounds of formula II wherein R^2 is other than alkoxy and C is thienyl, pyrazolyl, etc. having O/S links in view of the express equivalency teachings outlined above.

4. Claim 17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Myers et. al.** (US'969) in view of **McMahon et. al.** (US 6,649,635 B2). Athough Myers et. al. relate their compounds as tyrosine kinase (PTK) inhibitors, and is silent to the antiangiogenic effect or vascular permeability reducing effect, such a difference is not materially significant because it is well known in the art that the inhibition of PTK would inhibit cellular proliferation which in turn inhibits angiogenesis. See for example, the definition of a "disorder characterized by inappropriate PTK activity" cited on column 10, lines 52-62 of US'635 applied herein.

Claim Objections

5. Claims 11 and 12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 11 and 12 recite quinazoline species with substituent at the 7-position that is not taught or fairly suggested by the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M, T and Th (8:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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7-5-06